Edging ever closer to polio eradication

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After the triumphant announcement of the eradication of smallpox in 1980 to the World Health Assembly, the WHO soon switched its attention to polio prevention, instigating in 1988 the Global Polio Eradication Initiative—a highly productive public–private partnership between WHO, Rotary International, the US Centers for Disease Control and Prevention, UNICEF, and the Bill & Melinda Gates Foundation. By 1999, reports of wild type 2 polio had ceased, while type 3 disease left the world stage in 2012: impressive progress. Polio of any type has even stopped circulating in the hitherto strongholds of India and Nigeria; the last cases were reported in 2011 and 2014, respectively. Polio remains endemic only along the border of Pakistan and Afghanistan. Eradication seems in our grasp.

However, in May, 2012, the World Health Assembly noted an alarming reduction in control efforts by many at-risk countries and declared (the completion of) polio eradication to be a global public health emergency.[1] Recent successes had been tempered by the emergence of vaccine-derived polio viruses. Preventing the circulation of such viruses has become a pressing issue, especially type 2 which accounts for the great majority of isolates. In 2012, the WHO's Strategic Advisory Group of Experts on immunization promulgated a polio endgame strategy with some decisive recommendations whereby the "highest possible immunity" be achieved with one additional dose of inactivated polio vaccine (IPV) in concert with an "unchanged OPV routine schedule", but without the type 2 component in the oral polio vaccine (OPV). Beginning from April, 2016, a bivalent (types 1 and 3) OPV was to be substituted for the trivalent OPV, while delivering one dose of IPV concurrently with the third dose of bivalent OPV in the infant schedule.[2,3]

In *The Lancet Global Health*, Ed Clarke and colleagues[4] report a large, complex, but elegant phase 4 non-inferiority randomised trial in Gambian infants on the safety and immunogenicity of IPV given at age 9 months concurrently with a measles and rubella combined vaccine and yellow fever vaccine. Two different routes of administration were also assessed. A key study rationale derives from Clarke and colleagues' assertion that a second dose of IPV might be needed to optimise disease control in countries at risk of polio resurgence. For programmatic and immunological reasons, the likely best opportunity to deliver a second dose of IPV would be at age 9 months, when measles-rubella vaccination is already being delivered, as is yellow fever vaccine in countries with endemic yellow fever. The primary objective was to assess safety and to test for immunological interference associated with co-administration of IPV, measles-rubella, and yellow fever vaccines. Clarke and colleagues hoped to demonstrate non-inferiority of immune responses to concurrently delivered vaccines (IPV and measles-rubella; IPV and yellow fever; measles-rubella and yellow fever; and IPV, measles-rubella, and yellow fever) in comparison with study groups in which each of the three vaccines was given alone. The secondary objective was to address the immunogenicity and safety of IPV, full dose (0·5 mL) and fractional dose (0·1 mL), administered in the standard way by needle and syringe, or by disposable-syringe-jet-injector.

Dealing with straightforward issues first, all the vaccinations were well tolerated, with low levels of both local and systemic reactogenicity. Furthermore, global non-inferiority was shown for all the combinations of vaccines on the basis of seroprevalence and seroconversion data. However, examination of antibody titres found that not one vaccine combination achieved non-inferiority compared to the groups where each vaccine was given alone. This was due to reduced titres against both rubella and yellow fever upon any co-administration. The effect was greatest in the group in which all three vaccines were co-administered. By contrast, measles and polio responses were not reduced when vaccines were concurrently delivered.

Several concerns arise. Yellow fever vaccine is thought to induce long-term, probably lifelong, immunity but it is unclear whether the interference induced by co-administration will alter this. Continuing to observe the practice of giving a yellow fever vaccine booster every 10 years (or more) may obviate this concern, but that would be a backward step. Furthermore, reduced immunity to rubella may increase the proportion of at-risk females who enter the childbearing band and heighten the risk of congenital rubella syndrome. WHO recommends at least 80% coverage for each birth cohort, but more when rubella transmission is high or vaccine immunogenicity is reduced.[5]

The case for a second dose of IPV at 9 months, as outlined in this paper, is not compelling, but rejecting this new approach to vaccine delivery (and potentially improved disease control) because a subset of non-inferiority determinations are not achieved risks throwing out the baby with the bathwater. Given that this trial is the first to examine co-administration of IPV with measles-rubella and yellow fever vaccines (as well as measles-rubella and yellow fever co-administration), further work is certainly warranted, including studies in which a first dose of IPV is given at 3–4 months concurrently with the third OPV.

The responses to fractional dosing with IPV by either needle-and-syringe or disposable-syringe-jet-injector were reduced compared to the full dose. Clarke and colleagues soberly note that their data do not support implementation or widespread use of fractional doses, other than perhaps in an outbreak.

There is clearly intense interest by WHO, the Bill & Melinda Gates Foundation, and other organisations in improving the immunogenicity and practical deliverability of IPV vaccines. The recent publication of microneedle approaches in animals, achieving dose-sparing in at least one model, is encouraging and may lead to immunologically superior and more practical results in infants than using a jet injector to deliver vaccine intradermally.[6,7]

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